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Stereoselective Radical Reactions with Chiral Acrylamides and Methacrylamides

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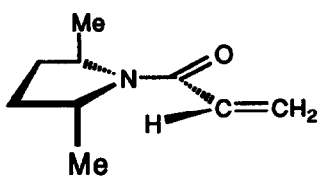
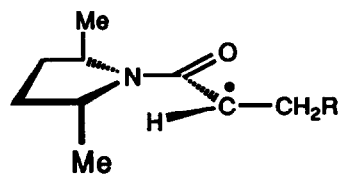
Abstract: *Stereoselective radical reactions are observed with chiral methacrylamides 3 and 7, although the π-systems are twisted to a considerable extent.*

Chiral amide groups can act as powerful auxiliaries in stereoselective radical reactions.[1] The reasons for their success may be explained by alkene **1** and radical **2** adopting preferred conformations in which the conjugated system is planar, and the small hydrogen atom adjacent to the amide group is *syn* to the amine. In this conformation of the C_2-symmetrical dimethylpyrrolidine, one of the two methyl groups is closer to the carbon atom α to the carbonyl group. Only this adjacent methyl group shields the sp^2-center effectively.[2]



1



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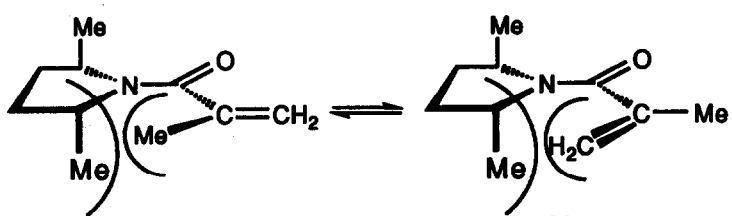
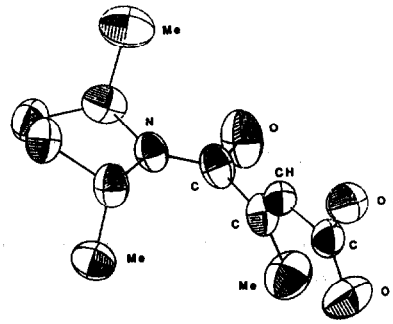
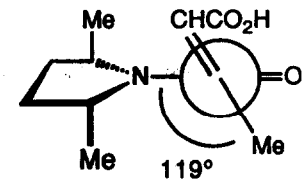


3a **3b**

Substitution of the hydrogen at the α-carbon atom by an alkyl group should have a considerable effect, because in both planar conformations **3a** and **3b** a carbon group is now in the sterically demanding location (*syn* to the amine). In fact, the X-ray crystal structure of the substituted alkene **4** shows that the α,β-unsaturated system is twisted with an out of plane angle of 119° (Figure 1).[3] Thus, the steric repulsion in the planar conformation is a more important factor than the stabilization by conjugation between the C,C- and C,O-π bonds.[4]

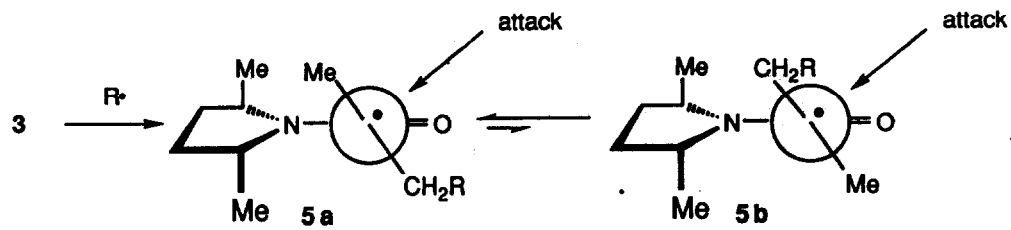




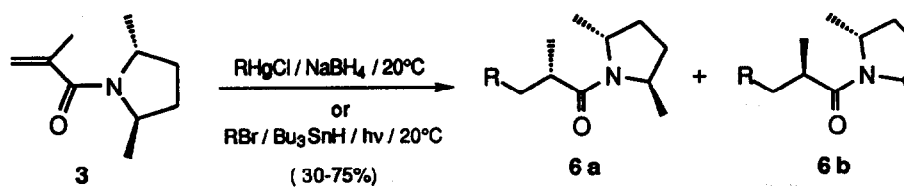
4

Figure 1. ORTEP-Plot and Newman projection of alkene **4**.

This twisting has a dramatic effect on the reaction rate. The addition of a *tert*-butyl radical to methyl acrylamide **3** is 37 times slower than to acrylamide **1** (20°C).[6] The intermediate of this reaction is radical **5**. According to AM1 calculations radical **5** is also twisted with **5a** and **5b** found as minimum conformations.[8]



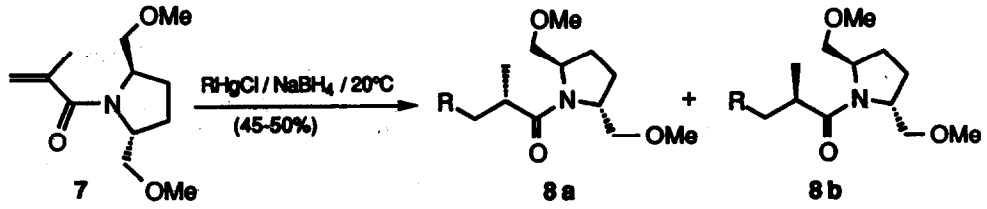
We were now interested to learn how this twisting influences the stereoselectivity of the radical hydrogen atom abstraction. Using the mercury or the tin method[9] the radical addition to methyl acrylamide **3** afforded **6a** as the main product.



R:	*t*-C_4H_9	90 : 10 (93 : 7, -10°C)
R:	*c*-C_6H_{11}	80 : 20
R:	CH_3	67 : 33

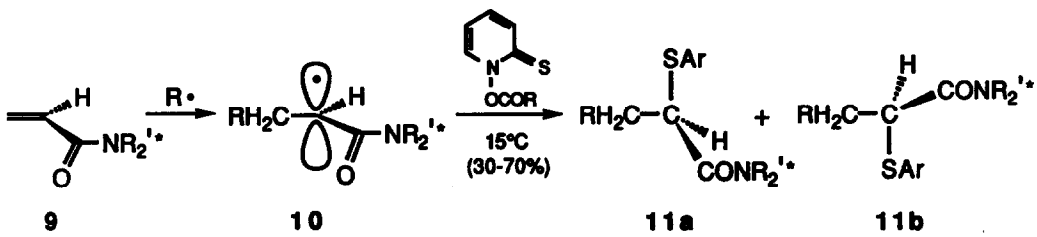
Thus, despite the twisting, the hydrogen atom abstraction step remains stereoselective. The stereoselectivity can best be explained by the preferred conformation **5a**, where reaction occurs *anti* to the shielding pyrrolidine group. In conformer **5a** the bulky RCH_2 substituent is further away from the sterically demanding pyrrolidine auxiliary and should be more stable than conformer **5b**.

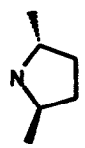
Both conformers are attacked *anti* to the pyrrolidine group and the stereoselectivity therefore depends on the equilibrium between **5a** and **5b**. The bulkier the group R is, the more conformer **5a** should be favored. In accord with this model the ratio **6a** : **6b** increases at 20°C from 67 : 33 for R = CH_3 to 80 : 20 for R = *c*-C_6H_{11}, and 90 : 10 (93 : 7, -10°C) for R = *t*-C_4H_9. A similar trend can also be observed with bis(methoxymethyl)pyrrolidine as auxiliary.[10]

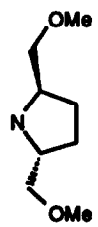


R: *t*-C_4H_9 9 : 91
R: *c*-C_6H_{11} 20 : 80

In contrast to the radical reactions with methyl acrylamides **3** and **7**, the acrylamide **9** shows no influence of group R on the diastereoselectivity. At 15°C, the diastereoselectivity is about 85:15 for R = *t*-C_4H_9, *c*-C_6H_{11}, and CH_3.[12] The intermediate of this reaction is the radical **10**, where the bulk of the prochiral CH_2R-group plays no role in the stereochemical process. The stereochemistry is only influenced by the methyl or methoxymethyl group at the chiral center of the pyrrolidine auxiliary.



$NR_2'^*$ =  R = *t*-C_4H_9, *c*-C_6H_{11}, CH_3 85 : 15

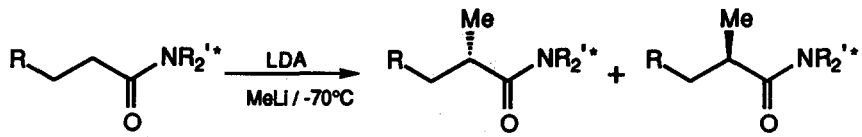
$NR_2'^*$ =  R = *t*-C_4H_9, *c*-C_6H_{11} 14 : 86

Conclusion: Although the tertiary radical **5** is twisted to a considerable extent it is attacked from the same side as the non-twisted secondary radical **10**. The added radical R influences the stereoselectivity of **5** because it affects the equilibrium between **5a** and **5b**.

Acknowledgement: This work was supported by the Swiss National Science Foundation.

References and Notes

1. For a review see: N.A. Porter, B. Giese, D.P. Curran, *Acc.Chem.Res.* **1991**, *24*, 296.
2. N.A. Porter, W.X. Wu, A.T. McPhail, *Tetrahedron Lett.* **1991**, *32*, 707.
   A. Veit, R. Lenz, M.E. Seiler, M. Neuburger, M. Zehnder, B. Giese, *Helv.Chim.Acta* in press.
3. The atomic coordinates for **4** and **11b** are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.
4. Twisted conformations of methacrylamides have also been observed by W. Oppolzer *et al.*[5a] and D.P. Curran *et al.*[5b] in related systems.
5. a) W. Oppolzer, G. Poli, C. Starkman, G. Bernadelli, *Tetrahedron Lett.* **1988**, *29*, 3559; b) D.P. Curran, T.A. Heffner, *J.Org.Chem.* **1990**, *55*, 4585.
6. The rel. rates were measured under pseudo-first order conditions.[7] A similar rate decrease with a twisted methacrylamide was observed by D.P. Curran *et al.*[5] in cycloaddition reactions.
7. B. Giese, G. Kretzschmar, J. Meixner, *Chem.Ber.* **1980**, *113*, 2787.
8. According to the AM1 calculations the energy differences between the conformations **5a** and **5b** is less than 1 kcal/mol. For AM1 calculations see: M.J.S. Dewar, E.G. Zoebisch, E.F. Healy, J.J.P. Stewart, *J.Am.Chem.Soc.* **1985**, *107*, 3902.
9. B. Giese, *Angew.Chem.Int.Ed.Engl.* **1985**, *24*, 553.
10. The structure of products **6a,b** and **8a,b** were elucidated *via* ionic methylation of the saturated amide **12** *via* the method of Katsuki.[11]



12 **6a** or **7a** **6b** or **7b**

At -78°C the ionic methylation of **12** (HNR_2'* = dimethylpyrrolidine) occurs with a d.e. of 97% (R = *t*-C_4H_9), 88% (R = *c*-C_6H_{11}) and 89% (R = CH_3). With bis(methoxymethyl)pyrrolidine as auxiliary only one isomer can be observed.

11. Y. Kawanami, Y. Ito, T. Kitagawa, Y. Tamiguchi, I. Katsuki, M. Yamaguchi, *Tetrahedron Lett.* **1984**, *25*, 857.
12. The reaction of the *tert*-butyl radical with **9** (HNR_2'* = dimethylpyrrolidine) has already been described: B. Giese, M. Zehnder, M. Roth, H.G. Zeitz, *J.Am.Chem.Soc.* **1990**, *112*, 6741. The structure elucidation of product **11b** (HNR_2'* = bis(methoxymethyl)pyrrolidine, R=*t*-C_4H_9) was carried out *via* X-ray analysis.[3]

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